UNITED STATES PATENT AND TRADEMARK OFFICE

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JUN 20 2007

Office of Regulatory Policy
HFD-7
5600 Fishers Lane (Rockwall II Rm 1101)
Rockville, MD 20857

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,674,860 was filed on September 19, 2006, under 35 U.S.C. § 156.

The assistance of your Office is requested in ascertaining whether the product identified in the present application, SYMBICORT® Inhalation Aerosol (formoterol fumarate dihydrate and budesonide), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period of 35 U.S.C. § 156(d)(1). Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our preliminary analysis of the application to date indicates that the subject patent would NOT be eligible for extension of the patent term under 35 U.S.C. § 156 unless the Food and Drug Administration considers the combination of budesonide and formoterol to be a single entity. According to the statute:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if —
>
> . . .
>
> (5)(A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;
>
> . . . .
>
> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product.
>
> . . .
>
> (2) The term "drug product" means the active ingredient of—
>
> (A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act)
>
> . . .
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

35 U.S.C. § 156.

It is noted that the electronic Orange Book accessed June 13, 2007, indicates the active ingredients as budesonide and formoterol fumarate dihydrate (a copy of the print out is attached). The term "product" as used in 35 U.S.C. § 156 includes any new drug or antibiotic drug, as a single entity or in combination with another active ingredient. See 35 U.S.C. § 156(f). "For a product which contains a plurality of active ingredients . . . the statute must be analyzed with respect to each active ingredient." See "Request for Patent Term Extension Final Decision," dated March 3, 1994, in U.S. Patent No. 4,529,601 (copy attached). If a drug product contains two active ingredients and both of the active ingredients have been previously approved, then regulatory review of the combination product cannot be relied upon for extension of a patent claiming the approved drug product. See In re Alcon Laboratories, 13 USPQ2d 1115 (Comm'r 1989). Since budesonide and formoterol have been previously approved individually, their use in a combination product does not appear to comply with 35 U.S.C. § 156(a)(5)(A), *i.e.*, the approval of SYMBICORT® would not appear to constitute the first permitted commercial marketing or use of the product as required by 35 U.S.C. § 156(a)(5)(A). Specifically, budesonide has been previously approved for use in products such as Pulmicort Respules®, Rhinocort® and Entocort® EC. Similarly, formoterol has been previously approved for use in Foradil® and Perforomist™. Thus, the combination product does not appear to constitute the first permitted commercial marketing or use of either active ingredient of the product. U.S. Patent No. 5,674,860 does not appear to be eligible for patent term extension based upon the regulatory review of SYMBICORT®. See also Fisons plc v Quigg, 8 USPQ2d 1491 (D.D.C. 1988).

Apparently in an effort to establish eligibility, Applicant attempts to rely on the Manual of Patent Examining Procedure ("MPEP") and asserts that since the product is a synergistic combination of budesonide and formoterol, it should be considered a single active ingredient for patent term extension purposes, and therefore be eligible for patent term extension under 35 U.S.C. § 156. Applicant is apparently relying on the MPEP at 2751 which states, "[f]urthermore, an approved product having two active ingredients, which are not shown to have a synergistic effect or have pharmacological interaction, will not be considered to have a single active ingredient made of the two active ingredients;" however, such reliance for eligibility is misplaced. This statement in the MPEP does not require that the USPTO treat an alleged synergistic combination drug product with two active ingredients as a single active ingredient made up of the two active ingredients for patent term extension purposes. Rather, the MPEP merely explains that a product having two active ingredients, without synergy, will not be treated as a single active ingredient. This does not imply that a showing of synergy in a product having two active ingredients, each of which was previously approved for commercial marketing or use, must be considered to be a single active ingredient for patent term extension purposes.

It is the position of the USPTO that a product which is nothing more than a combination of previously approved active ingredients fails to satisfy 35 U.S.C. § 156(a)(5)(A). Whether the product is a synergistic or nonsynergistic combination of active ingredients is of no consequence to a determination of compliance with 35 U.S.C. § 156(a)(5)(A). This position is supported by the decision of the Federal Circuit in Arnold Partnership v Dudas, 70 USPQ2d 1311 (Fed. Cir. 2004), where the court addressed whether a patent directed to a synergistic combination of drugs patents would qualify for a patent term extension under § 156. Specifically, the court stated, "[m]oreover, this court doubts that synergistic effects are an appropriate distinction for term extension policies, particularly where the statutory language does not distinguish at all between synergistic and nonsynergistic combinations."

Therefore, the approval for SYMBICORT® referenced in the application for patent term extension does not appear to represent approval as "the first permitted commercial marketing or use of the product" as required by § 156(a)(5)(A), and U.S. Patent No. 5,674,860 is **ineligible** for extension.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Leslie Morioka
Patent Department
White & Case LLP
1155 Avenue of the Americas
New York, NY 10036-2787

Search results from the "OB_Rx" table for query on "021929."

Active Ingredient:	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE
Dosage Form;Route:	SPRAY, METERED; INHALATION
Proprietary Name:	SYMBICORT
Applicant:	ASTRAZENECA
Strength:	0.08MG/INH;0.045MG/INH
Application Number:	021929
Product Number:	001
Approval Date:	Jul 21, 2006
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE
Dosage Form;Route:	SPRAY, METERED; INHALATION
Proprietary Name:	SYMBICORT
Applicant:	ASTRAZENECA
Strength:	0.16MG/INH;0.045MG/INH
Application Number:	021929
Product Number:	002
Approval Date:	Jul 21, 2006
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2007
Patent and Generic Drug Product Data Last Updated: June 13, 2007

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 08317407 **Filing Dt:** 10/03/1994 **Patent #:** 5674860 **Issue Dt:** 10/07/1997

PCT #: NONE **Publication #:** NONE **Pub Dt:**

Inventors: CHRISTER C. G. CARLING, JAN W. TROFAST

Title: COMBINATION OF A BRONCHODILATOR AND A STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS

Assignment: 1

Reel/Frame:	Received:	Recorded:	Mailed:	Pages:
008546 / 0050	06/18/1997	06/09/1997	07/17/1997	4

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: AKTIEBOLAGET ASTRA **Exec Dt:** 06/30/1994

Assignee: ASTRA AKTIEBOLAG
S-151 85 SODERTALJE, SWEDEN

Correspondent: WHITE & CASE
RICHARD STERNER
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

Search Results as of: 06/09/2007 08:46 AM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: February 22, 2007 v.2.0

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE COMMISSIONER OF PATENTS AND TRADEMARKS

In re Astra Lakemedel Aktiebolag	:	REQUEST FOR PATENT
U.S. Patent No. 4,529,601	:	TERM EXTENSION
	:	
_____	:	FINAL DECISION

An application for extension of the term of U.S. Patent No. 4,529,601 has been filed under 35 USC § 156. The application raises a question of eligibility for patent term extension of a patent claiming two active ingredients in a drug product (EMLA Cream) that was approved for commercial marketing and use by the Food and Drug Administration (FDA), where each of the active ingredients had been approved separately for commercial marketing and use in previous regulatory reviews by the FDA. For the reasons set forth below, the application is denied.

Facts

The application for extension of the term of U.S. Patent No. 4,529,601 granted July 16, 1985, which claims a human drug product containing a specific mixture (by weight) of lidocaine and prilocaine, was filed in the Patent and Trademark Office (PTO) on February 26, 1993. The application was filed by the patent owner Astra Lakemedel Aktiebolag (Astra).

EMLA Cream is a drug product that was approved for commercial marketing and use by the FDA on December 12, 1992, pursuant to § 505 of the Federal Food, Drug and Cosmetic Act. The approved product, a homogeneous cream which contains a mixture of lidocaine and prilocaine in specified weight proportions, was approved as a topical anesthetic for local anesthesia. Lidocaine and prilocaine are well known anesthetics, each of which had previously been independently approved as a topical anesthetic for local anesthesia.

The '601 patent claims prilocaine in admixture with lidocaine in a specified weight ratio. Astra admits (Appl., p. 2) that lidocaine and prilocaine have previously been approved by the FDA as separate compounds, but submits that the claimed product sets forth a distinct and novel active ingredient. Astra argues the active ingredient in EMLA Cream is "the eutectic mixture that results from combining lidocaine and prilocaine in the specified weight proportions." Astra asserts:

> The novelty of this active ingredient is demonstrated by the synergistic effect of the resulting eutectic mixture in the form of an oil which gives EMLA Cream improved deep penetrating effects and improved anesthesia which surpasses the topical anesthetic effect of either lidocaine or prilocaine alone when each is administered as a separate compound [or] when administered together in two different formulations (Appl., p. 2).

On August 31, 1993, Astra submitted a letter (with Attachments A-C and Exhibits A1-A6) in support of the application for extension. In the letter Astra repeats its contention that EMLA Cream contains a new distinct and novel active ingredient. Astra states that both lidocaine base and prilocaine base exist in crystalline form at room temperature, but when the crystalline bases of lidocaine and prilocaine are mixed with each other a physio-chemical change takes place and a eutectic mixture results in the form of an oil that has a melting point below room temperature, and therefore, both lidocaine and prilocaine exist as a liquid oil rather than as crystals . Astra asserts that this oil constitutes the new distinct and novel active ingredient. Astra states that this is because once the oil is formed, the individual ingredients, lidocaine and prilocaine, are no longer physically distinguishable, and that individually, lidocaine and prilocaine do not penetrate the intact skin to produce anesthesia but EMLA Cream readily penetrates the intact skin to produce anesthesia.

Astra further argues that the FDA recognized the single active ingredient character of EMLA Cream because it waived its fixed combination prescription drug policy as defined in 21 CFR § 300.50 on the ground that the mixture is sufficiently unique that an exception to satisfy the combination drug policy seems warranted. Astra states on page 6 of the letter:

> By waiving the applicability of the fixed combination drug policy the FDA acknowledged that EMLA Cream does not have two active ingredients. Rather, EMLA Cream has a new distinct and novel active ingredient, a eutectic mixture in the form of an oil which is created when a physico-chemical change takes place upon mixing the crystalline forms of lidocaine base with prilocaine base. Thus, EMLA Cream meets the requirements of Section 156.

Discussion of Eligibility Criteria For Patent Term Extension

The starting point for statutory interpretation is the plain language of the statute. Unless it is ambiguous, the language Congress chose is conclusive of its meaning absent a clearly stated contrary intention. Burlington Northern R.R. v. Oklahoma Tax Comm'n, 481 U.S. 454, 461 (1987). See also Glaxo Operations UK Ltd. v. Quigg, 894 F2d 392, 395, 13 USPQ2d 1628, 1630 (Fed. Cir. 1990) (absent a "clearly expressed legislative intention to the contrary," a statute's plain meaning "must ordinarily be regarded as conclusive"). Statutory words are normally presumed, unless the contrary appears, to be used in their ordinary and usual sense, and with the meaning commonly attributed to them. Calminetti v. United States, 242 U.S. 470, 485 (1917) (the meaning of a statute must, in the first instance, be sought in the language in which the act is framed and, if that is plain, the sole function of the court is to enforce it according to its terms).

Under 35 USC § 156(a) a term of a patent which claims a product shall be extended if, inter alia, the product has been subject to a regulatory review period before its commercial marketing or use. In addition, under § 156(a)(5)(A):

> ... the permission for the commercial marketing or use of the product ... is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; (Emphasis added.)

Thus, the determination of eligibility of U.S. Patent No. 4,529,601 turns on the provisions in § 156(a)(5)(A) that the permission for the commercial marketing or use is the first permitted commercial marketing or use of the product. The term "product" is defined in 35 USC § 156(f) as follows:

> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product. ...
>
> (2) The term "drug product" means the active ingredient of -
>
> (A) a new drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ...
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient. (Emphasis added.)

Where, as in the present case, no salts or esters of the active ingredients are involved, the definition of "product" set forth in § 156(f) (substituted within brackets for "product et seq." in § 156(a) and for "product" in § 156(a)(5)(A)) applies to the patent term extension requirements of §§ 156(a) and 156(a)(5)(A) as follows:

> § 156(a) The term of a patent which claims [the active ingredient ... , as a single entity or in combination with another active ingredient] ... shall be extended ... if -
>
> (5)(A) ... the permission for the commercial marketing or use of [the active ingredient ... , as a single entity or in combination with another active ingredient] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ... , as a single entity or in combination with another active ingredient] under the provision of law under which such regulatory review period occurred;

The statute says active ingredient, not active ingredients. Thus, eligibility for patent term extension under § 156(a) requires that the patent claims the active ingredient of a new drug, as a single entity or in combination with another active ingredient. Section 156(a)(5)(A) permits patent term extension based on FDA approval of the active ingredient as a single entity or in combination with another active ingredient, provided it is the first FDA approval of the active ingredient, as a single entity or in combination with another active ingredient.

For a product which contains a plurality of active ingredients, as here, the statute must be analyzed with respect to each active ingredient. Active ingredient, as defined in § 156(f), is singular and the definition of "human drug product" explicitly recognizes that the "active ingredient" may be used "in combination with another active ingredient" to embrace a human drug product with a combination of active ingredients. If the term "active ingredient" was interpreted to include a plurality of active ingredients, the phrase "including any salt or ester of the active ingredient" would not make any sense because there is no such thing as a salt or ester of two ingredients. A statute should be construed, if possible, to avoid absurd results. United States v. Turkette, 452 U.S. 576 (1981).

Application of Eligibility Criteria to '601 Patent and EMLA Cream

The following facts are either admitted by Astra or supported by the record: (1) the active ingredient lidocaine was previously approved under § 505 for obtaining local anesthesia; (2) the

active ingredient prilocaine was previously approved under § 505 for obtaining local anesthesia; and, (3) EMLA Cream is the first product that contains both the active ingredients lidocaine and prilocaine to be approved under § 505 for obtaining local anesthesia.

The determination of eligibility of the '601 patent for patent term extension turns on the provisions of § 156(a)(5)(A). Astra argues the combination of lidocaine and prilocaine in the specified weight proportions is a new "active ingredient" which was approved for the first time. The FDA advises the PTO that EMLA Cream was approved through a regulatory review period as a product containing the two previously approved "active ingredients" lidocaine and prilocaine rather than as a new chemical entity resulting from the combination of these active ingredients. In a letter dated August 4, 1993, the FDA states:

> The active ingredients in EMLA Cream, lidocaine and prilocaine, have both been previously approved and EMLA Cream contains no new chemical entity. In fact, EMLA Cream was approved through a regulatory review period, as defined under 35 U.S.C. § 156(a)(4), based on the fact that EMLA Cream is a product containing the two previously-approved drugs of lidocaine and prilocaine rather than as a new chemical entity resulting from these active ingredients. Therefore, the applicant's claim that EMLA Cream presents a "distinct and novel active ingredient" does not appear to be supported by FDA's records. [Emphasis added.]

The record does not support Astra's claim that a new active ingredient is present. Astra's assertion on page 2 of the application that the eutectic mixture of lidocaine and prilocaine in the form of an oil has a synergistic effect resulting in improved anesthesia surpassing the anesthesia effect of lidocaine and prilocaine alone or together in different formulations is contradicted by the reports and background materials contained in the record. In its telefax transmission to the FDA on August 23, 1989, describing the analgesic effectiveness of EMLA Cream (Exh. A-4, ¶ 4), Astra states:

> It is known ... that both drug substances [lidocaine and prilocaine] penetrate the epidermis and enter the dermis of the skin where ... pain receptor nerve endings ... are located. No claim is made for any synergistic action or for any other pharmacological interaction between the two active local anesthetics. The only implied claim is that both agents contribute in some degree to the block of neuronal structures in the skin .... [Emphasis added.]

Astra's claim that a new active ingredient is present in EMLA Cream is further diluted in its letter of November 1, 1989, to the FDA (Exh. A-5, p. 2):

> It may be useful to keep in mind that EMLA is a formulation of two thoroughly studied and widely used local anesthetics. ... EMLA is able to act effectively at considerably reduced doses of lidocaine and prilocaine simply because its eutectic nature makes for a more efficient percutaneous migration of these substances. The lidocaine and prilocaine remain the same (as in other formulations) in every chemical particular; and the amounts of these substances available systemically from recommended doses of EMLA 5% Cream are similar to those systemically available from doses of these substances approved for relatively simple and routine dentistry. [Emphasis added.]

Astra further argues that the fact that the FDA decided to waive its fixed combination drug policy (21 CFR § 300.50) shows that the FDA acknowledged that EMLA Cream does not have two active ingredients. The Combination Drug Policy of § 300.50 is used in determining the type of evidence required for approval of fixed combination drugs. A decision to waive the requirements of § 300.50 is not tantamount to a holding that no combination of drugs is present. If no combination were present, § 300.50 would not be applicable and there would be no reason to waive the rule. The record (Exh. A-4, ¶¶ 8-16) clearly shows that Astra, in response to the FDA's request for a comparison study of EMLA Cream, a lidocaine cream and a prilocaine cream, argued that such comparative testing would not be valid comparison because of the compositions of the respective creams. Astra points out that EMLA Cream contains no solvent oil which is present in both lidocaine and prilocaine creams, which oil plays a role in the release rate of the anesthetic. In response to Astra's arguments, the FDA (Attachment C) decided that because, inter alia, of the apparent difficulty in obtaining an appropriate single ingredient control preparation (Attachment C, ¶ E), the mixture is sufficiently unique and an exception to satisfying the Combination Drug Policy seemed warranted. The FDA's subsequent decision not to require the proposed comparative study did not constitute a decision that a new active ingredient was present in EMLA Cream and no combination was present. On the contrary, because the FDA saw a need to apply (and, in the present case, waive) § 300.50, shows the FDA considered EMLA Cream to be a combination with lidocaine and prilocaine both present, but that the unique nature of the combination warranted a waiver of § 300.50.

The '601 patent claims the combination of active ingredients lidocaine and prilocaine contained in EMLA Cream. Under § 156(a)(5)(A), as it pertains to the active ingredients claimed in the patent (lidocaine and prilocaine), the patent would be eligible for patent term extension if:

> ... the permission for the commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] under the provision of law [§ 505 of the Act] under which such regulatory review period occurred;

Here, the patent is not eligible because each of the active ingredients claimed in the patent and present in the approved product (lidocaine and prilocaine) previously were permitted to be commercially marketed and used under the same provision of law [§ 505 of the Act] under which such regulatory review period for EMLA Cream occurred. The approval of EMLA Cream did not represent the first permitted commercial marketing or use of either of the active ingredients in EMLA Cream under § 505 of the Act.

The fact that the approval of EMLA Cream represents the first time that the combination of lidocaine and prilocaine was permitted to be commercially marketed or used by the FDA does not give rise to eligibility for patent term extension. The statute is clear that patent term extension is permitted under § 156(a)(5)(A) only if the approval of the active ingredient is the first approval of the active ingredient - i.e., no previous approvals of the active ingredient have occurred as a single entity or in combination with another active ingredient. As noted above, both lidocaine and prilocaine have been approved by the FDA as single entities prior to the approval of EMLA Cream. Clearly, the approval of EMLA Cream does not represent the first approval of either lidocaine or prilocaine.

Legislative History Supports the PTO Position

The '601 patent is not eligible for patent term extension because the permission for commercial marketing or use of EMLA Cream was not the first permitted commercial marketing or use of the active ingredients claimed in the patent within the meaning of §156(a)(5)(A). This position is consistent with the statute, including the statutory definition of the term "product" in § 156(f), and the legislative history of the statute.

From the beginning of the congressional debate that led to enactment of § 156, attention focused on the decline of effective patent life for new chemical entity (NCE) drugs. In re Alcon Laboratories Inc., 13 USPQ2d 1115, 1119 (Comm'r Pats 1989). Congress adopted the focus on NCE's when it proscribed patent term extension [§ 156(a)(5)(A)] if the active ingredients had received permission for commercial marketing or use in regulatory review periods that were concluded prior to a subsequent regulatory review period upon which the application for patent term extension is based. If the active ingredients had already received permission for commercial marketing from the FDA under the same provision of law, they would not be considered to be an NCE in a subsequent regulatory review period whether the active ingredients are used alone or in combination with other active ingredients. According to a report by the House Committee on Energy and Commerce accompanying H.R. 3605, 98th Cong., 2d Sess. (1983):

> Paragraphs [(a)(4)] and [(a)(5)] describe two conditions which must be met by the product which is claimed in the product patent to be extended .... First, the product must have been subjected to a regulatory review period under an applicable federal law, and approved, before the product was allowed to be commercially marketed. ... Second, ... the approved product must have been approved for commercial marketing for the first time. The Committee's bill requires extensions to be based on the first approval of a product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs. These drugs had been approved by the Food and Drug Administration (FDA) for the first time. (Emphasis added.)

H.R. Rep. No. 98-857, Part I, 98th Cong., 2d Sess. 37-38 (1984), reprinted in 1984 U.S. Code Cong. & Admin. News 2671.

The legislative history shows that Congress intended that the condition expressed in § 156(a)(5)(A) should apply to the product [active ingredients] claimed in the patent [§ 156(a)], and that patent term extension should be available only to active ingredients that are NCE's which have been approved by the FDA for the first time. The only evidence showing that patent time had been lost in the regulatory review process before the FDA related to NCE drugs.

Thus, the legislative history of § 156 shows that Congress intended to grant patent term extension only to those products [active ingredients] classified by the FDA as class I new chemical entities under FDA's long-standing drug classification system. [A copy of the FDA

Staff Manual Guide No. CDER 4820.3, dated January 22, 1992, describing the IND/NDA Classification System is attached to this decision.] According to this classification system, Type I drugs are new molecular entities - i.e., the active moiety (that part of the chemical compound that is responsible for the drug's therapeutic effect) is not yet marketed either as a single entity or as part of a combination product. Type 1 drugs are contrasted to other types which are directed to new salts, esters or derivatives of active moieties (Type 2), new formulations (Type 3), new combinations of drugs not previously marketed together (Type 4), already marketed drug products (Types 5 and 6) and drugs already marketed but without an approved NDA (Type 7). These Types are not mutually exclusive, but where the drug product falls into more than one category, all appropriate categories are reflected in the overall classification for the drug.

Congress found no evidence relating to new combinations of old active ingredients, old active ingredients administered in a new dosage form and no evidence relating to an old active ingredient approved for a new indication (use) that would justify patent term extension based on products of these types. As noted in Fisons plc v. Quigg, 876 F.2d 99, 10 USPQ2d 1869 (Fed. Cir. 1989), there is strong support in the legislative history of § 156 for the interpretation of § 156(a)(5)(A) adopted by the PTO that patent term extension is available only to drug products that are NCEs - i.e., active ingredients that have been approved for the first time by the FDA.

Each of the active ingredients lidocaine and prilocaine contained in the approved product EMLA Cream was a well known local anesthetic that had been independently approved for commercial marketing and use prior to FDA approval of EMLA Cream for use as a local anesthetic. Since both active ingredients had been previously approved, neither lidocaine, prilocaine, nor their combination was a new chemical/molecular entity at the time of FDA approval of EMLA Cream.

Accordingly, it is consistent with the legislative history of § 156 that a patent claiming a combination of two active ingredients, both of which were previously approved as local anesthetics, be denied patent term extension based on a later approval of a drug product containing the combination for use as a local anesthetic, notwithstanding any enhanced effect of the combination.

Decision

The PTO concludes that U.S. Patent No. 4,529,601, which claims a combination of the active ingredients lidocaine and prilocaine in the approved product EMLA Cream, is not eligible for patent term extension under § 156. Accordingly, the application for extension is denied because the permission for commercial marketing or use of lidocaine and prilocaine in EMLA Cream was not the first permitted commercial marketing or use of lidocaine or prilocaine under the provision of law [§ 505 of the Federal Food, Drug and Cosmetic Act] under which regulatory review of EMLA Cream occurred. 35 USC § 156(a)(5)(A).

Date: 03 March 1994

C. E. Van Horn

Charles E. Van Horn
Patent Policy & Projects Administrator
Office of the Assistant Commissioner for Patents

Edward V. Filardi
White & Case
1155 Avenue of the Americas
New York, NY 10036-2787

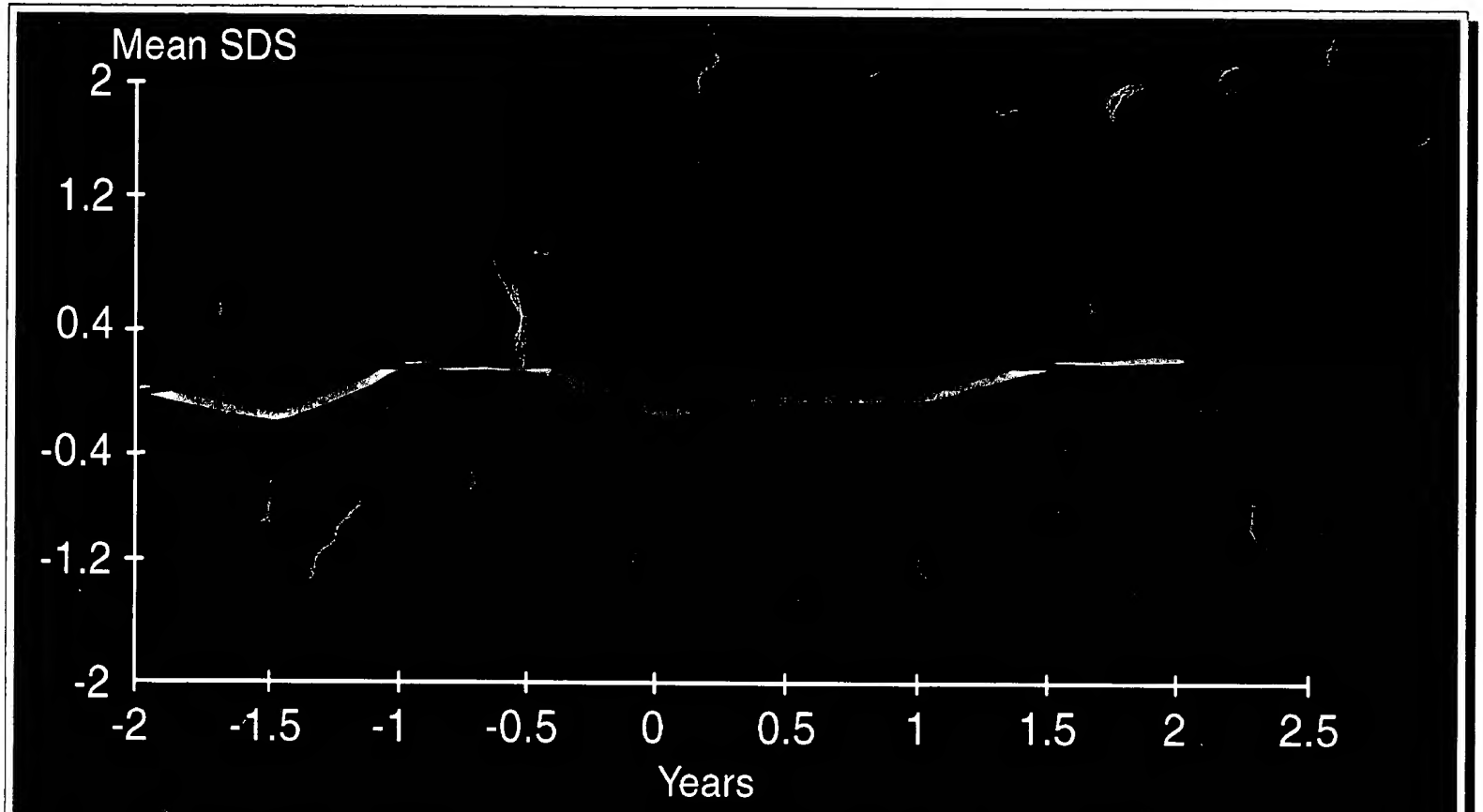
(For Astra)

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 11-44
Rockville, MD 20857

Re: EMLA Cream

FDA Docket No. 93E - 0130

Safety Aspects of Budesonide in Children



Mean height standard deviation score in 176 children. During the first 2 years no exogenous budesonide was given (176 child.) Then 124 children started to inhale budesonide at a mean dose of 650µg/day, while the remaining 52 continued without any inhaled steroid. *There was no significant difference in growth rate between the two groups at any point in time.*

S. Pedersen, Eur.Respir.Rev. 4(17), 33-43 (1994)

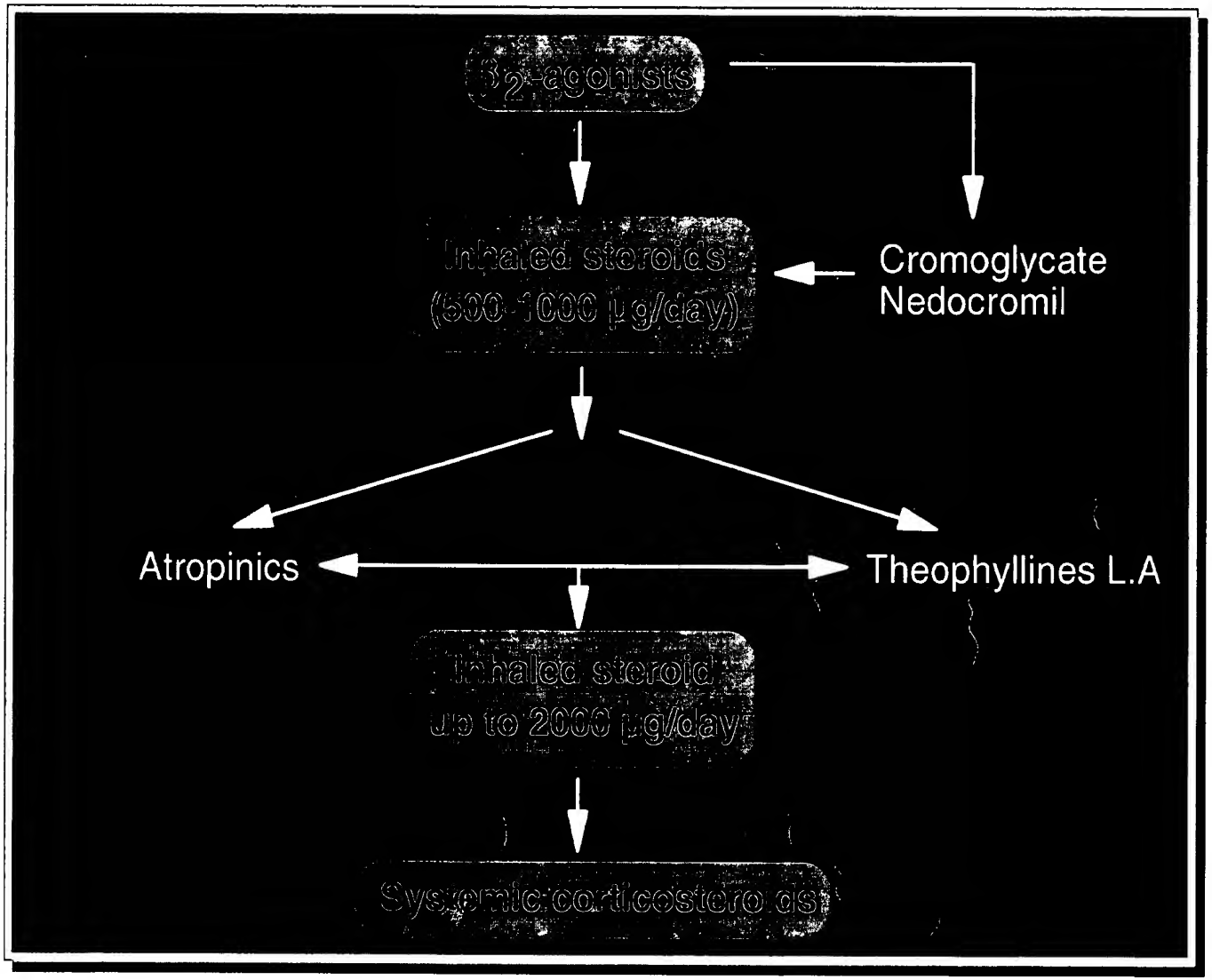
Conclusion

Asthma mortality and morbidity are unacceptably high. The reason may be an overreliance on bronchodilators, with underuse of inhaled and oral corticosteroid treatment and failure to make objective measurements of severity together with inadequate supervision i.e poor compliance.

The profile of formoterol has surprisingly been found to be well suited for administration together with the glucocorticosteroid budesonide - recently proved to be very safe - in the treatment of asthma. By administration in a single inhalation device, multiple medications and frequent-dose regimens necessary for asthma treatment have been reduced to a minimum. By doing so a synergistic effect consisting of a better patient compliance will be obtained. The better compliance gives an improved disease control and thereby a higher quality of life for the patient.

The fixed combination of formoterol/budesonide is new.

Scheme of Long-Term Treatment of Chronic Asthma



J.H Marsac, Annals of Allergy 63 (1989), 220-4

Guidelines on the Management of Asthma

Stepwise approach to asthma therapy

Step 1	Inhaled β_2-agonist on demand
Step 2	Low dose inhaled antiinflammatory Steroid/ cromoglycate/ nedocromil
Step 3	High dose inhaled steroid
Step 4	Additional bronchodilator Long acting inhaled β_2-agonist Oral theophylline/ β_2-agonist Inhaled anticholinergic
Step 5	Maintenance oral steroids

Combination vs Fixed Combination Therapy
Two Approaches in the Treatment of Asthma

Fixed combination of a β_2-agonist and a steroid

- Advantages: Convenience of replacing two inhalers with one - ensuring treatment with the steroid by simplification of the treatment regimen - most patients need both but forget to use one - improved compliance - better disease control

- Disadvantages: Flexible use of the individual components

Fixed dose combination therapy in the treatment of asthma
The case against it

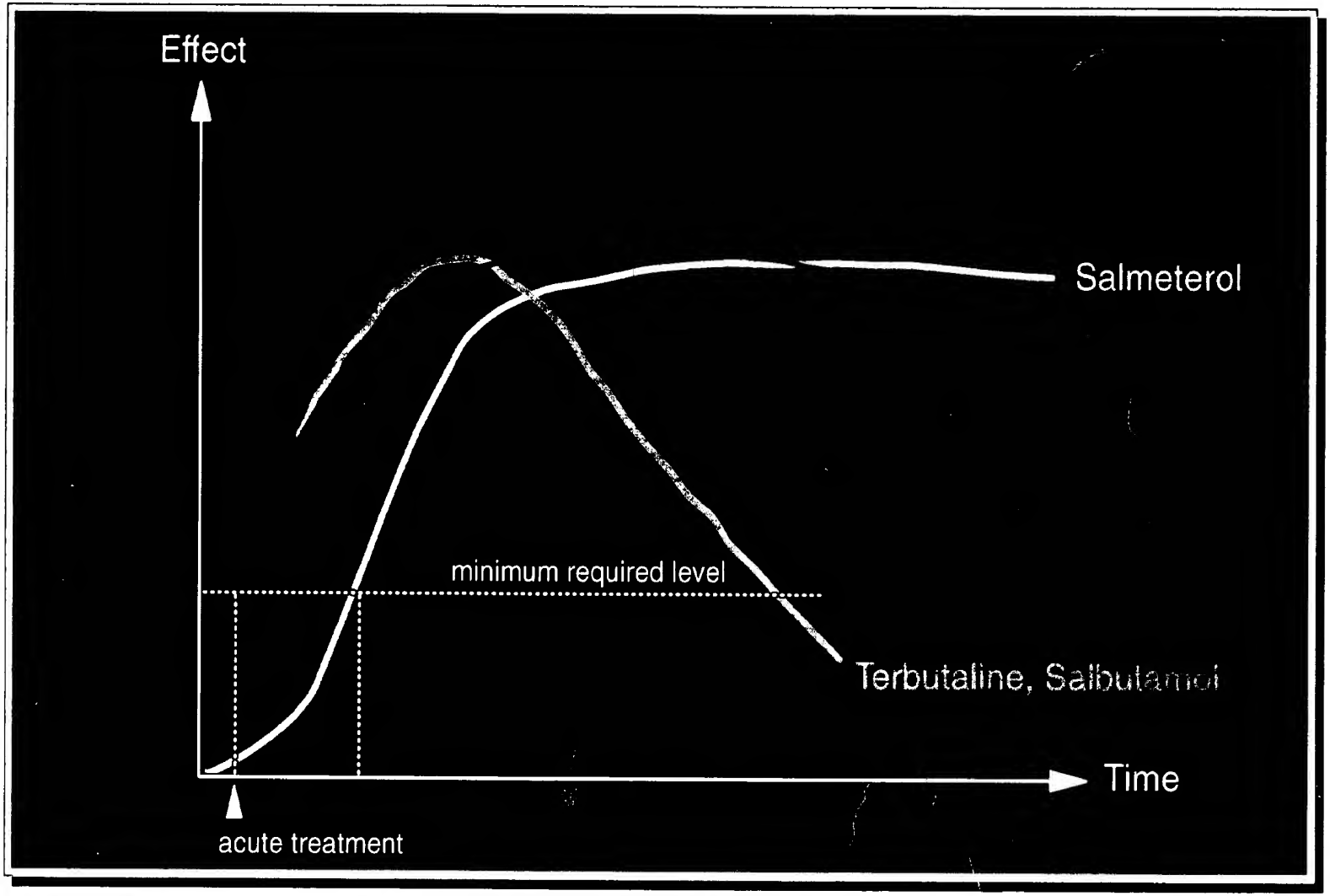
by

David A. Lindsay (Director of medicine)

"In an excellent review paper, Gillian Shenfield (1982) stated: «There is no longer any place for fixed combination bronchodilators...» I agree with her, and believe that a similar statement is appropriate for fixed combinations of BDP and beta-agonists".

Mechanisms in asthma: Pharmacology, Physiology and Management (1988), pages 421-425.

Schematic Representation of Fast Onset (Formoterol) and Slow Onset (Salmeterol) β_2-agonists

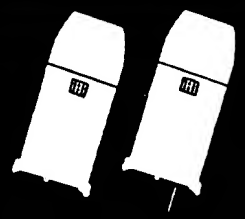


Patient compliance

Most physicians assume that once the diagnosis is made and the prescription order is written, the patient will benefit from his diagnostic and therapeutic acumen. Unfortunately, drug treatment of any kind is often compromised by lack of full compliance by the patient. Patients are less likely to use the medications as directed.

Multiple medications, frequent-dose regimens, and the physical features of the medication itself often foster poor compliance.

Combination vs Fixed Combination Therapy
Two Approaches in the Treatment of Asthma



Combination of a β_2-agonist and a steroid

- Advantages: Flexible use of the individual components
- Disadvantages: Many patients can not cope with using two individual inhalers - less compliance -less disease control